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Review Article

An overview of liver cirrhosis - pathophysiological mechanisms

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Abstract. Liver cirrhosis is the last stage of fibrogenesis – a process developed on the background of chronic aggressions on the liver. The most common causes of liver cirrhosis are chronic alcohol consumption and chronic infections with hepatic viruses. In the last decade, there has been an increase in both prevalence and mortality due to this disease. Complications developed because of liver cirrhosis are often responsible for a considerable number of deaths. The pathophysiology of cirrhosis is mostly explained by hepatic insufficiency, a condition that causes, in evolution, a generalized suffering of the body – multiple organ failure. The main complications are due to portal hypertension: ascites and collateral circulation – manifested mainly by esophageal varices. Hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, clotting disorders, endocrine system dysfunction, malnutrition and sarcopenia are only some examples of the vast range of complications encountered in liver cirrhosis. Although the diagnosis of this disease can be made precocious by paraclinical tests, the symptoms are present only in the decompensated stage of the disease, revealing a poor prognosis. Treatment for patients suffering from liver cirrhosis is often palliative; despite considerable advances in medical research, the only curing treatment remains liver transplantation.

Key Words: liver cirrhosis, diagnosis, complications, management

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Introduction

Hepatic cirrhosis is a histological diagnosis – a complete tissue disorganization, meaning the appearance of hepatocytic regeneration nodules, surrounded by fibrous septa. This disease develops on the background of some chronic liver pathologies, in the context of the persistence of the etiological factor. Liver cirrhosis occurs as a result of the progressive and persistent deposition of collagen fibers, because of one incorrectly/insufficiently treated chronic hepatitis. The alteration of the tissue architecture has consequences both on the macroscopic aspect of the liver, which becomes nodular, with a bumpy surface, and on the functions of the liver; liver failure outlines the clinical picture and complications of this pathology, not only at the hepatic, but also at the systemic level (Sharma & John 2022).

Etiology

There are multiple causes incriminated for the development of liver cirrhosis, most of them being represented by chronic alcohol consumption, chronic infections with hepatic viruses B, C, D and non-alcoholic fatty liver disease. Other less common causes are: primitive biliary cholangitis, autoimmune hepatitis, hemochromatosis, Budd-Chiari syndrome, Wilson's disease, consumption of hepatotoxic drugs (e.g. methotrexate) or substances with increased liver toxicity (carbon tetrachloride), deficiency of α-1 antitrypsin, cystic fibrosis, galactosemia, glycogenosis, hepatic venous congestion and others; liver cirrhosis can also be idiopathic (Chen et al 2020; Foster & O'Brien 2021).

Epidemiology

Recent studies have shown, on the one hand, a decreasing trend in the prevalence of liver cirrhosis of viral B and C etiology, and, on the other hand, an increase in the prevalence of liver cirrhosis caused by non-alcoholic fatty liver disease and excessive alcohol consumption. In 2017, 5.2 million new cases of liver cirrhosis were reported, with an equal distribution by gender, and in 2019, an increase in mortality due to liver cirrhosis was observed by 8.1% compared to 2017, totaling 1,48 million deaths (Liu & Chen 2022).

Pathophysiology

Liver fibrosis is the key element due to which morphological and functional changes occur in the liver, in the context of liver cirrhosis. The liver responds to any kind of aggression by inflammation; therefore, Küpffer cells, endothelial cells, platelets and damaged hepatocytes produce pro-inflammatory cytokines such as TGF-β1, PDGF, ET-1, MCP-1. Under the action of pro-inflammatory cytokines, the Ito cells, also called hepatic stellate cells, activate and initiate the deposition of collagen fibers, an action in which fibroblasts and myofibroblasts also take part. Proinflammatory cytokines exert a chemotactic effect on the cells responsible for their secretion and also on other inflammatory cells (T lymphocytes, plasmocytes, eosinophils, neutrophils), therefore amplifying the inflammation in the liver. The fibrogenesis is a complex and long-lasting process that goes through several stages, the last one (stage IV) representing liver cirrhosis.

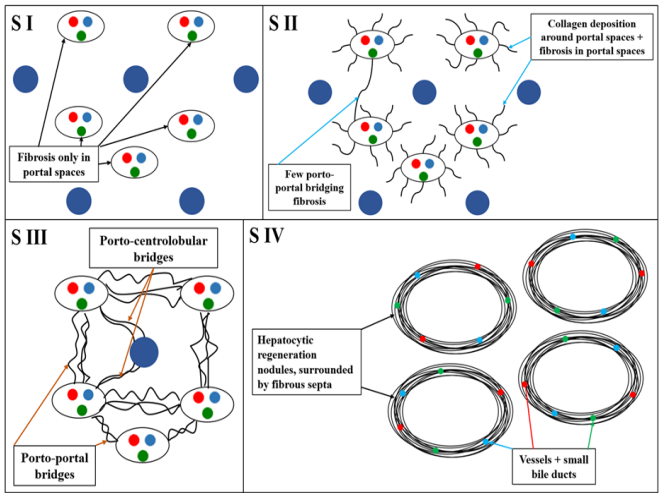

Fig. 1. Fibrogenesis

The deposition of type I and III collagen fibers starts from the stage of chronic hepatitis and goes through four phases, which we illustrated in figure 1 (Tanțău et al 2016).

Liver failure often develops because of liver cirrhosis and it is characterized by troubles in protein, lipid and carbohydrate metabolism, acid-base and hydroelectrolytic balance, and finally – multiple organ dysfunction syndrome (MODS). The reduced hepatic synthesis is reflected by hypoalbuminemia; compensatory, the α and β globulins increase. Coagulation disorders cause prolongation of the Quick time, due to the deficiency of vitamin K-dependent coagulation factors – II, VII, IX, X. The disseminated intravascular coagulation is another consequence of insufficient protein synthesis, but not only, because to its physiopathology contribute also the reduced synthesis of fibrinolysis inhibitors and coagulation inhibitors: protein C, S and antithrombin III. The coagulation troubles can be amplified by the associated thrombocytopenia – in the context of hypersplenism, which sometimes develops secondary to liver cirrhosis. Inadequate uptake of amino acids by the liver produces hyperammonemia; the toxic effect of ammonia on the central nervous system can cause hepatic encephalopathy. Impairment of lipid metabolism occurs due to intrahepatic cholestasis (because of fibrosis); thus, free cholesterol and lipoprotein X are increased in serum. In ethanolic liver cirrhosis, triglyceride synthesis increases by the release of fatty acids from adipose tissue. Depending on the early or advanced stage of liver cirrhosis, hyper- or hypoglycemia occurs. Hyperglycemia is determined by the inadequate uptake of glucose by hepatocytes, in the initial stages, whereas hypoglycemia is the result of impaired gluconeogenesis, in the advanced stages of liver failure. Acid-base imbalances consist in the development of respiratory alkalosis and metabolic acidosis. Liver failure can sometimes lead to multiple organ failure, in which case patients might develop heart failure. Right heart failure causes rapid pulmonary circulation, which makes breathing difficult. The compensatory response is represented by hyperventilation, which, through the increased elimination of carbon dioxide, causes respiratory alkalosis. Heart failure, because it induces hypoxia and the transition to anaerobic metabolism, causes an increase in the level of lactic acid in blood; its accumulation contributes to the onset of metabolic acidosis. Dilution-induced hyposodemia occurs through activation of the RAAS (renin-angiotensin-aldosterone

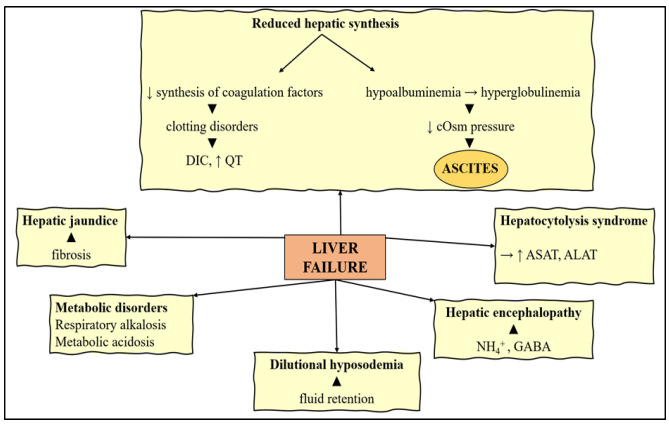

Fig. 2. Liver failure

system), with successive fluid retention. Malfunction of the Na+/K+ pump in hepatocytes, caused by hepatic cellular dysfunction, contributes to hyponatremia (Schuppan & Afdhal 2008. Regarding the immune status of patients suffering from liver cirrhosis, recent studies have demonstrated immunosuppression, reflected by impaired function of both innate and adaptive immunity. The immunosuppression marker was the Torque teno virus, detected by PCR; although it is frequently present in the general population and is not associated with any type of pathology, in patients with liver cirrhosis – an intense replication of this virus can be detected, suggesting immunosuppression. A reduced ability of CD4+ and CD8+ T lymphocytes of responding to stimulation by producing pro-inflammatory cytokines has been reported. Immunophenotyping made possible the detection of low frequencies of natural killer lymphocytes in patients with acute decompensation of liver cirrhosis. Figure 2 illustrates the main manifestations present in case of liver failure (Rueschenbaum et al 2021).

Morphopathology

Depending on the size of the regeneration nodules, the cirrhotic liver has a micro-, macronodular or mixed appearance. Micronodular liver cirrhosis is characteristic of alcoholic etiology, cystic fibrosis, primitive biliary cirrhosis and hemochromatosis. Macronodular cirrhosis is frequently encountered in cirrhosis of viral etiology, drug toxicity and in Wilson's disease; inside some large nodules, there may be normal acini. Microscopically, fibrosis is observed (Foster & O'Brien 2021).

Clinical picture

The clinical picture is given by the compensated or decompensated state of liver cirrhosis. In compensated liver cirrhosis, patients are often asymptomatic, the disease being detected only by the altered results of specific paraclinical tests. The presence of characteristic signs and symptoms reveals the decompensated state of liver cirrhosis; they result from the generalized liver dysfunction and the associated portal hypertension. Portal hypertension can lead patients to present with ascites, spontaneous bacterial peritonitis, umbilical hernia, or variceal hemorrhage – sometimes life-threatening (Foster & O'Brien 2021). Collateral circulation causes the classic "caput medusae" aspect, as described in literature. The Cruveilhier-Baumgarten sign appears in the context of portal hypertension, as a murmur in the

epigastric region. Hepatic encephalopathy is clinically diagnosed by the presence of fetor hepaticus, altered mental status and asterixis (Sharma & John 2022). Patients with liver cirrhosis are often malnourished, complain of have muscle cramps and present sarcopenia (Lai et al 2021). In some cases, hepatocellular carcinoma is detected; we mention that liver cirrhosis is a frequent but not mandatory state for the development of hepatocarcinoma. Sometimes, in liver cirrhosis, clubbing, Terry nails, Muehrcke nails, or azure lunules (in Wilson's disease) may appear (Sharma & John 2022).

Complications

Complications in liver cirrhosis are explained by complex pathophysiological mechanisms; the most important of them have as common pathogenesis – the portal hypertension. Portal hypertension developed secondary to liver cirrhosis is due to the action of two different components: mechanical and dynamic. The mechanical component is represented by liver fibrosis, which causes increased resistance to blood flow in the portal venous system. The dynamic component refers to the vasoconstriction of intrahepatic veins, which is based on two mechanisms: the synthesis of substances that exercises an α2-adrenergic action (e.g. endothelin, angiotensin II) and the lack of response to the vasodilatory action of nitric oxide. Splanchnic vasodilation, produced as a result of the nitric oxide effect, activates the renin-angiotensin-aldosterone system, the sympathetic nervous system and the increase in the release of vasopressin; these processes result in the installation of hypervolemic status and hyperdynamic circulation. An attempt to reduce pressure in the port venous system involves the development of collateral circulation, but, despite this compensatory mechanism, the portal hypertension is maintained due to increased splenic blood flow. Collateral circulation develops as porto-systemic shunts, and the most common manifestation of it is the appearance of esophageal varices. Esophageal varices can break, causing massive upper digestive hemorrhages (KASL 2018). Ascites appeared because of liver cirrhosis represents a fluid transudation in the peritoneal cavity. The pathophysiological mechanisms that trigger the development of ascites are represented by low osmotic colloid pressure due to hypoalbuminemia, increased hydrostatic pressure in the spleen capillaries and liver sinusoids, attributed to the imbalance of the Starling forces, hydrosaline retention (RAAS) and increased pressure in the hepatic capillaries; the latter, combined with an inefficient lymphatic drainage, due to an exaggerated lymphatic volume that exceeds the physiological possibilities of drainage, make the lymph pass through the Glisson capsule to the peritoneal cavity. In the context of severe liver damage, the quality of the intestinal barrier is altered, with an increased intestinal permeability and an ineffective intestinal immunological response. This makes possible the passage of microorganisms through the portal vein to the liver, which causes the activation of Toll receptors; the result of these processes is inflammation. The ineffective immunological response, along with a deficiency of the complement system in the ascites fluid can cause the major complication of ascites – the spontaneous bacterial peritonitis. Important splenomegaly, often present secondary to liver cirrhosis, develops as a result of splenic venous hypertension, in the context of portal hypertension. Figure 3

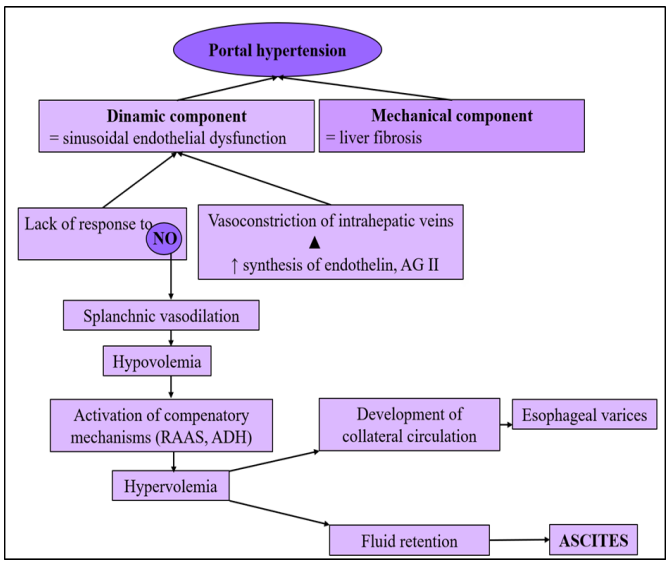

Fig. 3. Pathophysiology of portal hypertension

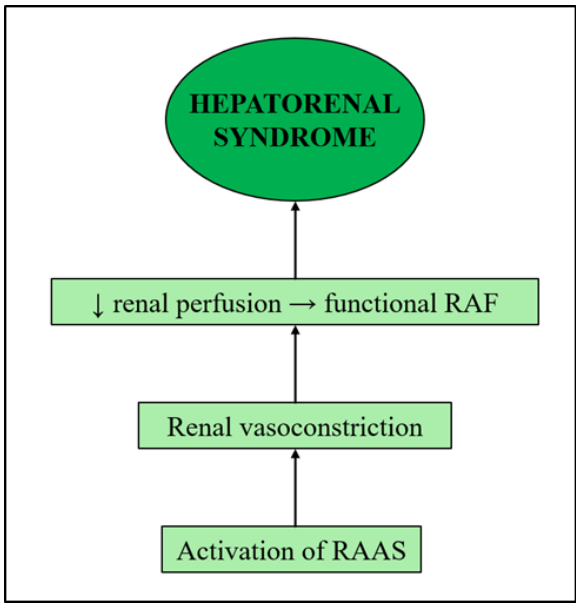

Fig. 4. Hepatorenal syndrome

shows schematically the pathophysiology of portal hypertension (KASL 2020).

Hepatic encephalopathy is another complication of liver cirrhosis. This occurs due to increased permeability of the blood-brain barrier. The inability to exercise the detoxification function of the liver causes the accumulation of ammonium ions in the blood. At neuronal level, ammonium ions alter the transmembrane passage of water, electrolytes and amino acids and have an inhibitory effect on the excitatory and inhibitory postsynaptic potential. To the neuronal inhibitory effect of ammonium ions, the inhibitory effect on the central nervous system of γ-aminobutyric acid is added, the level of which increases in blood due to inefficient hepatic clearance, caused by liver failure. Cerebral edema sometimes occurs in case of hepatic encephalopathy, because of the increased vascular permeability and of the effects of neurotoxins (KASL 2020).

Hepatorenal syndrome occurs as a result of low renal perfusion and is therefore a type of renal failure of pre-renal cause. Insufficient renal perfusion, combined with renal vasoconstriction

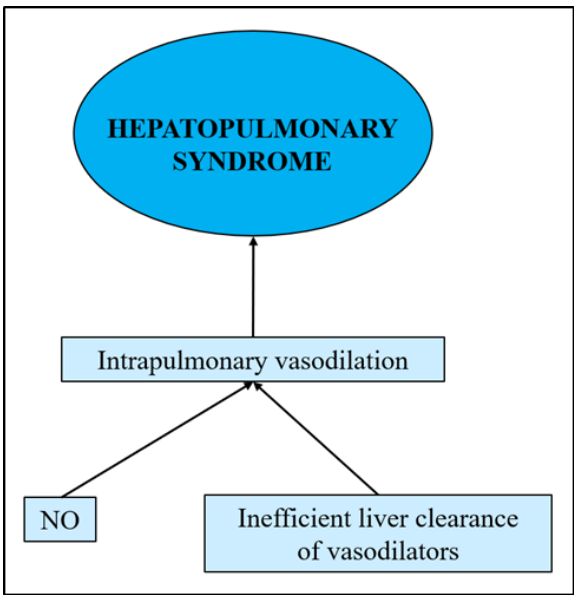

Fig. 5. Hepatopulmonary syndrome

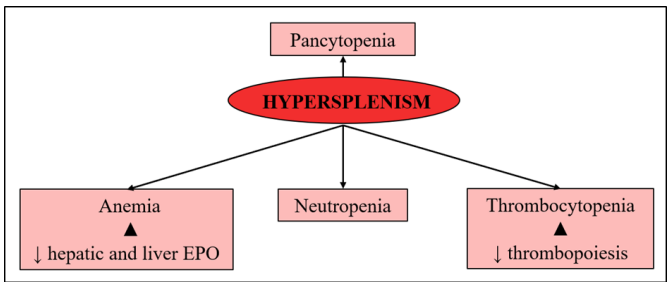

Fig. 6. Hypersplenism

which cannot be combated by the synthesis of certain substances that exercise a renal vasodilating action, cause hypoxic manifestations, such as acute tubular necrosis. Figure 4 shows schematically the hepatorenal syndrome (Lata 2020).

Hepatopulmonary syndrome has as an important pathophysiological mechanism – the intrapulmonary vasodilation, which occurs due to increased synthesis of nitric oxide in the lung, but also because of the inefficient liver clearance of vasodilators synthesized in excess by the cirrhotic liver. Hepatopulmonary syndrome is clinically manifested by hypoxemia, the development of intrapulmonary and pleural arteriovenous shunts (causing pleural effusion), pulmonary hemorrhages and atelectasis. Figure 5 illustrates hepatopulmonary syndrome (Sharma & John 2022).

Liver cirrhosis causes hematological complications. Anemia can occur through various mechanisms; it is a consequence of both insufficient production of erythropoietin in the liver and kidneys (in the context of hepatorenal syndrome) and hypersplenism developed secondary to liver cirrhosis. Normocytic normochromic anemia is a characteristic of chronic diseases, but macrocytic normochromic anemia is especially encountered in hepatic cirrhosis of ethanolic etiology, due to folic acid deficiency. Anemia also occurs due to the decrease of circulating free testosterone. Hypersplenism often causes pancytopenia. Thrombocytopenia in the context of hypersplenism causes disorders of primary hemostasis. The synthesis deficiency of coagulation factors causes disorders of secondary hemostasis. Figure 6 shows the main effects of hypersplenism (Sharma & John 2022).

Malnutrition and sarcopenia are frequently present in liver cirrhosis. The mechanisms incriminated are the malabsorption, the inefficient protein synthesis – which determines the catabolic use of muscle proteins, the consequence being the decrease of muscle mass, with the installation of fatigue and altered capacity at sustained physical exercise. Muscle cramps are the result of the production of lactic acid, due to anaerobic metabolism (Lai et al 2021).

The homeostasis of the endocrine system is altered in patients suffering from liver cirrhosis. There is an increased sensitivity to estrogen and reduced sensitivity to testosterone. Hyperestrogenemia is the main cause of the appearance of spider nevi and palmar erythema; in men, gynecomastia, hypogonadism, disappearance of secondary sexual characteristics and sexual dysfunction may occur. In women, hyperestrogenemia can manifest itself through infertility, amenorrhea and irregular menstrual cycles (Sharma & John 2022).

Paraclinical data

Ultrasonography is the simplest and most non-invasive imaging technique. Collagen fibers and steatosis appear hyperechogenic in the US. Ultrasonographical, we can appreciate the irregular surface of the cirrhotic liver and the ratio between the width of the caudate/hepatic right lobes, which is frequently increased in liver cirrhosis. Through the Doppler mode, the liver arterial vessels, liver veins and the port venous system are evaluated. Using US, the hepatocellular carcinoma can be observed, but the diagnosis cannot be made only through the US, because further exploration is required. One-dimensional transitory elastography/Fibroscan, appreciates the stiffness of the liver, using high velocity ultrasound; it is a valuable indicator of liver fibrosis and is increasingly used for the diagnosis of liver cirrhosis, at the expense of liver biopsy (picrosirius red coloring is used to highlight collagen fibers), which it cannot replace. A recorded value over 13kPa in FibroScan diagnoses liver cirrhosis. FibroScan is difficult to apply to patients with ascites and/or increased abdominal circumference.

Hepato-splenic scintigraphy using technetium-99m sulfur colloid demonstrates an increased uptake of tracer in the bone marrow and spleen compared to the liver; this examination may help making the diagnosis of liver cirrhosis.

Computer tomography can detect hepatosplenomegaly and dilated collateral vessels from liver cirrhosis. Early arterial wash-out on contrast CT examination is a valuable indicator for the diagnosis of hepatocarcinoma. Magnetic resonance imaging (MRI) is superior to CT, but more expensive and less available. It can detect iron deposits and fatty liver, as well as possible biliary tract formations/obstructions. Hemangiomas, as well as other benign tumors, are easily highlighted by MRI.

Superior digestive endoscopy is a diagnostic and therapeutic method for esophageal and gastric varicose veins, allowing their ligation, sclerotherapy and injection of vasoactive substances (terlipressin, octreotide, somatostatin) in case of hemorrhage (Sharma & John 2022; Chen et al 2019).

Treatment

Treatment of liver cirrhosis is often palliative and addresses complications in particular. If the cause of the disease is identified,

Table 1. Common lab analysis

Section	Parameters	Possible results in liver cirrhosis
Complete blood count	Erythrocytes	↓, due to anemia
	Hemoglobin	↓, due to anemia
	Erythrocytes indices	Normal – normochromic normocytic anemia
		MCV ↑ – macrocytic anemia
	ESR	↑ due to anemia
	Reticulocytes	Normal or increased (post superior digestive hemorrhage)
	Platelets	↓ due to hypersplenism +/- the medullary suppressant effect exerted by alcohol
	Leucocytes	↓ due to hypersplenism +/- the medullary suppressant effect exerted by alcohol
	Neutrophiles	↑ in case of bacterial peritonitis
Protein electrophoresis	Proteins	↓, due to deficient synthesis
	Albumins	↓; poor prognosis if < 28 g/dl
	α globulins	↑ compensatory and in case of bacterial peritonitis or ↓ in case of severe liver damage
	β globulins	↑ compensatory or ↓ in case of severe liver damage
	γ globulins	↑ due to inappropriate liver clearance
Liver function	Quick time	↑ due to the deficiency of coagulation factors
Biochemistry	ALAT	↑ by hepatocytolysis
	ASAT	↑ by hepatocytolysis
	Total bilirubin	↑ in cholestasis, due to fibrosis
	ALP	↑ in cholestasis, due to fibrosis
	γ-GT	↑ if there is associated cholestasis
	5'-nucleotidase	↑ in cholestasis
	Free cholesterol	↑ by cholestasis
	Triglycerides	↑ by release from adipose tissue
Electrolytes	Na^+	↓ in dilutional hyponatremia
Renal function	Creatinine	↑ in case of renal damage; if > 1,5 mg/dl – poor prognosis
	Urea	↓ by insufficient synthesis

etiological treatment is preferable; some examples include: antiviral therapy in viral hepatic cirrhosis, stopping alcohol consumption in ethanolic cirrhosis, corticosteroids for autoimmune hepatic cirrhosis, ursodeoxycholic acid in primary biliary cirrhosis. Patients diagnosed with type B viral infection should be treated with Lamivudine, Entecavir and Tenofovir; the antiviral properties of these substances, plus the improved liver function and the antifibrotic effect recommend them as a valuable therapeutic line. In patients diagnosed with type C viral infection undergoing effective antiviral treatment, a stopping in the progression of liver fibrosis and the risk of progression to hepatocellular carcinoma has been described. Other substances with antifibrotic effects are angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. The treatment administered in order to prevent bleeding from esophageal varices and to reduce the severity of portal hypertension includes nonselective β-blockers (propranolol, nadolol, carvedilol) and isosorbide-mononitrate (Yoshiji et al 2021). Treatment of ascites involves the administration of albumin and diuretics; during paracentesis, albumin is required to prevent circulatory collapse (Bai et al 2022). In patients with refractory ascites, peritoneovenous shunt (PVS) or transjugular intrahepatic portosystemic shunt (TIPS) is performed (Yi et al 2022). Patients with hepatorenal syndrome are administrated norepinephrine in combination with albumin in order to ensure an adequate circulating plasma volume. Splenectomy or partial splenic embolization may be useful in case of pancytopenia. Metformin can be used in case of insulin resistance; this drug has been shown to prevent complications associated with liver cirrhosis and to stop carcinogenesis. In the case of hepatocellular carcinoma, the first line of treatment remains liver resection (for solitary tumors); ablation can be used for tumors less than 3 cm associated with CTP (see below) A or B. Liver transplantation is a valid therapeutic option for small tumors developed on a liver with severe dysfunction (Yoshiji et al 2021). The diet should be balanced and supplemented with vitamins, especially vitamin B6 and B12 – in the

Table 2. Diagnostic explorations

Biomarkers	**HBsAg, HBeAg, HBV-DNA, HBsAg antibodies, HBeAg antibodies, anti-HBc antibodies of type IgM or IgG**	**Used to detect a viral infection with hepatitis B virus**
	anti-HDV antibodies of type IgM or IgG, HDV-RNA	Used to detect HBV + HDV coinfection/ HDV superinfection
	HCV-RNA, anti-HCV antibodies	Used to detect a viral infection with hepatitis C virus
	ANA, ASMA, ALKM-1	Autoimmune hepatitis
	AMA (Antimitochondrial antibodies)	Primary biliary cholangitis
	Ferritin, transferrin	Hemochromatosis
	Ceruloplasmin, urinary cuprum	Wilson's disease
	α_1-antitripsin, α-fetoprotein	Hepatocarcinoma
Diagnostic tests	***FibroTest:***	> 0.75 → diagnostic test for liver cirrhosis
	· α_2-macroglobulin	
	· haptoglobin	
	· A_1 apolipoprotein	
	· total bilirubin	
	· γ-GT	
	· age	
	· gender	
	FibroMeter:	> 1 → diagnostic test for liver cirrhosis
	· α_2-macroglobulin	
	· hyaluronic acid	
	· ALAT	
	· ASAT	
	· total bilirubin	
	· γ-GT	
	· platelets	
	· Quick time	
	Hepascore	> 0.84 → diagnostic test for liver cirrhosis
	· α_2-macroglobulin	
	· hyaluronic acid	
	· total bilirubin	
	· γ-GT	

case of ethanolic hepatic cirrhosis. Daily salt intake should not exceed 2 g/day. Aspirin and non-steroidal anti-inflammatory drugs must be avoided or used with caution, due to the risk of gastrointestinal bleeding to which they predispose, but also to renal toxicity – if the patient also suffers from hepatorenal syndrome. The recommended daily protein intake is 1.2-1.5 g/kg/day, and in case of malnutrition – branched chain amino acids are administered (Puri et al 2021); these amino acids are also useful in treating hepatic encephalopathy, along with probiotics, rifaximin, supplemental zinc and carnitine (Grüngreiff et al 2021). As adjuvant treatments, hepatoprotective drugs have been described, of which we mention Ganoderma Lucidum extract (Chen et al 2018). Most of the time, despite the vast therapeutic options that currently exist, liver transplantation remains the only curative treatment (Foster & O'Brien 2021).

Prognosis

The prognosis of patients with liver cirrhosis is extremely variable and refers to survival. The prognosis mostly depends on the existence and severity of the associated complications (Sharma & John 2022). There are several scores used to assess prognosis and survival, the best known being Child-Turcotte-Pugh (CTP) and MELD (model of end-stage liver disease). CTP takes into account ascites, hepatic encephalopathy, bilirubin, albumin and Quick time. The more advanced the CTP, the lower the survival. CTP A (<7 points) predicts a 82% survival rate at 1 year, 45% at 5 years and 25% at 10 years. CTP B (7-9 points) predicts a 62% survival rate at 1 year, 20% at 5 years and 7% at 10 years. CTP C (>10 points) predicts a 42% survival rate at 1 year, 20% at 5 years and 0% at 10 years. The MELD score takes into account bilirubin, INR and creatinine. A MELD score <10 signifies a

1-year survival rate of 97%, whereas a MELD score between 30 and 40 signifies a 1-year survival rate of only 70%. The survival rate after liver transplant at 1 year and 5 years is 85% and 72% (Foster & O'Brien 2021; Peng et al 2016). Patients with liver cirrhosis and associated hepatocellular carcinoma have a more reserved prognosis than patients with cirrhosis of the liver (Pinter et al 2016). A recent study showed more pronounced alteration of liver biochemical tests in patients with hepatic cirrhosis and concomitant COVID-19 infection, than in patients with liver cirrhosis not infected with SARS-CoV2 virus, as well as in patients with COVID-19 infection without liver cirrhosis (An et al 2021). At the same time, some authors, in a retrospective study in hospitalized SARS-CoV2 infected patients, showed that biochemical alteration and high liver fibrosis score were associated with a more severe COVID-19 evolution and a higher mortality rate (Crisan et al 2021). Survival after liver transplantation may be influenced by the recurrence of some diseases on the transplanted liver (Foster & O'Brien 2021).

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